REMARKS

Claims 1-16 and 18-24 are pending. Claims 1-3, 6-9, 12, 14, 15, and 18-24 are under consideration. Claims 4, 5, 11, 13, and 16 are drawn to a nonelected species. Claims 1-3, 6-9, 12, 14, 15, and 18-24 stand rejected for obviousness over Klunk et al. (U.S. Patent No. 6,417,178; hereafter "Klunk 1") in view of Klunk et al. (Life Sciences 1998 63:1807-1814; hereafter "Klunk 2") and Huang et al. (Somatic Cell and Molecular Genetics 1998 24:217-233; hereafter "Huang").

Independent claims 1 and 2, from which all other rejected claims depend, are directed to methods of decreasing cell death or toxicity or decreasing aggregate or inclusion formation as a result of expanded polyglutamine repeats by administering Congo red (diphenyldiazo-bis-alpha-naphthylaminesulfonate) or a pharmaceutically effective derivative. An exemplary disease caused by expanded polyglutamine repeats is Huntington's disease. Applicants traverse the obviousness rejection.

As stated in the previous reply, to support an obviousness rejection, the Office must put forth a *prima facie* case that meets the legal standard for obviousness found in M.P.E.P. § 2142, which states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re*

Vaeck, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991) (emphasis added).

Applicants again assert that the Office has failed to establish a *prima facie* case of obviousness in the present case as the cited references fail to provide motivation to combine or modify the references, and there is no reasonable expectation of success.

There is no motivation to combine the references

Klunk 1 discloses the use of Chrysamine G in treating various amyloid diseases. Klunk 2 teaches that Chrysamine G inhibits Aβ induced toxicity in cells. And Huang discloses staining techniques employing Congo red. Applicants assert that there is no motivation to combine these references to achieve the instant invention.

The motivation provided by the Office is that "cited prior arts teaches that Congo red and the Congo red analogues employed in [Klunk 1] are known to be similarly useful as amyloid binding agents for reducing toxicity, one of ordinary skill in the art would have seen the employment of Congo red for the utility disclosed in '178." The Office acknowledges that Klunk 1 alone does not provide any motivation to employ Congo red in a treatment for amyloid diseases and instead relies on Klunk 2 to show the equivalence of amyloid binding of Congo red and Chrysamine G. The Office relies on Huang only for two facts: "Congo red binding to the amyloid from Huntington disease; and amyloid from Huntington disease has expanded polyglutamine repeats." Applicants assert that the Office's characterizations of Klunk 2 and Huang are incorrect.

Klunk 2 discloses results relating only to Aβ. As stated in the previous reply, teachings on Aβ are irrelevant to the patentability of instant claims 1 and 2, which are directed to treatments of polyglutamine repeats. Regarding these comments on Klunk 2, the Office states that "expanded polyglutamine repeats would read on Aβ diseases." This statement is factually incorrect. It appears that the Office is incorrectly equating the terms "amyloid" and "Aβ." Amyloid refers to a deposit of peptides or proteins. Aβ is a specific amyloid plaque formed from APP and is believe to be a causative factor in the development of Alzheimer's disease pathology. Aβ does not contain an expanded polyglutamine repeat. In support of this position, Applicants have enclosed U.S. Patent No. 6,743,427 (see col. 10, ll. 31-43) showing the amino acid sequence of Aβ, which contains only a single glutamine (Gln). It is indisputable that diseases caused by Aβ and diseases caused by polyglutamine repeats are entirely separate. Therefore, the ability of Congo Red to bind to Aβ has no bearing on its potential as a therapeutic for diseases caused by polyglutamine repeats. Indeed, Huang suggests that "*in vivo* huntingtin aggregates have a complexity greater than the amyloid deposits seen in other disorders, such as Alzheimer's disease" (page 229, first column). Thus, the Office has failed to provide any motivation to combine teachings on binding of compounds to Aβ and binding of compounds to polyglutamine repeats.

Regarding the teachings of Huang, the Office states that it was only cited for two facts: "Congo red binding to the amyloid from Huntington disease; and amyloid from Huntington disease has expanded polyglutamine repeats." That Huntington's disease

involves polyglutamine repeats is acknowledged by Applicants. In reply to the Office's other assertion, Applicants note that nowhere does Huang teach that Congo red binds to *in vivo* amyloid from Huntington's disease, as presently claimed by Applicants. Indeed as stated in the previous reply, Huang clearly states that "Congo red has not proved valuable for visualizing intraneuronal [i.e., *in vivo*] inclusions in HD brain" (*Id.*). The Office has therefore failed to show that Congo red binds to *in vivo* polyglutamine repeat aggregates.

In addition to the deficiencies of the motivation provided by the Office, each of Klunk 1, Klunk 2, and Huang teach away from employing Congo red in a method of treating polyglutamine repeats. In dismissing these arguments from the previous reply, the Office relies on *In re Gurley*, on the theory that a composition does not become patentable because "it has been described as somewhat inferior to some other product for the same use." Applicants assert that *In re Gurley* is not relevant to the instant case, because Congo red is not merely described as somewhat inferior – it is described as unusable. For example, Klunk 1 states that Congo red does not enter the brain (col. 4, lines 57-59), and, for this reason, Chrysamine G is employed in treatments for amyloidosis. Klunk 2 further states that Congo red does not enter the brain in significant quantities (abstract). Regarding Klunk 2, the Office states that "Congo red ... is nevertheless useful [as] an amyloid binding agents, and is able to enter brain." The irrelevance of Congo red binding to Aβ amyloid, as disclosed in Klunk 2, is discussed above. Regarding the Office's assertion that Congo red is able to enter the brain, nowhere does Klunk 2 make such a claim. Klunk 2 only states that Congo red does not

enter in significant quantities. Finally, Huang states that Congo red does not bind to *in vivo* huntingtin aggregates (page 229, first column), thereby further teaching away from its therapeutic use. The Office also states that Applicants have not provided evidence that Congo red does enter the brain. Such evidence is irrelevant to the motivation to combine, as it is the Office's burden to establish a *prima facie* case of obviousness, and Applicants are not required to provide evidence to support arguments based on the plain teachings of the cited art.

In summary, the Office has not shown that the prior art teaches that Congo red and Chrysamine G are equivalent for treating polyglutamine repeats or that the art teaches that Congo red even binds to *in vivo* polyglutamine repeats. The Office has therefore provided no motivation for combining the references. In addition, the cited references clearly teach away from the use of Congo red in a method to treat polyglutamine repeats. The rejection should be withdrawn.

There is no reasonable expectation of success.

The Office did not respond to Applicants' arguments regarding the reasonable expectation of success requirement for an obviousness rejection. Applicants therefore reiterate and expand on their previous arguments. As stated above and in the previous reply, both Klunk 1 and Klunk 2 explicitly state that Congo red is unsuitable as a therapeutic agent because of its purported inability to enter the brain. Klunk 1 states that Congo red does not enter the brain (col. 4, lines 57-59), and Klunk 2 states that Congo red

does not enter the brain in significant quantities, i.e., it enters, if at all, in insignificant quantities. Klunk 2 further states that the ability to enter the brain well is important for therapeutic activity (page 1808). Huang, as discussed above, teaches that Congo red is ineffective as a stain for *in vivo* huntingtin aggregates. The art relied on by the Office thus teaches that Congo red neither enters the brain well, a requirement for therapeutic efficacy, nor binds to *in vivo* polyglutamine repeats. The cited art cannot therefore provide a reasonable expectation of success, as required by law.

In sum, none of the cited references provides a motivation to combine or modify the reference teachings, and, based on these references, there is no reasonable expectation of success. Accordingly, the rejection of claims 1-3, 6-9, 11, 12, 14, 15, and 18-24 for obviousness should be withdrawn.

Information Disclosure Statement

Applicants note that the Form PTO-1449 that was submitted with a Supplemental Information Disclosure Statement filed on February 26, 2004 has not been initialed and returned, and hereby request that it be initialed and returned with the next Office action.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying for one

month, to and including July 26, 2004, and a check in payment of the required extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: July 26, 2004

for J. Cooper McDonald

Kristina Bieker-Brady, Ph.D., P.C.
Reg. No. 39,109

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

J. Cooper McDonald, Ph.D.
Patent Agent
Reg. No. 52,011